REMARKS

Amendments to the Specification

Applicants have amended the Specification to include material that was incorporated by reference in the Specification as filed. Applicants are filing a Declaration concurrently stating that the material added by amendment consists of portions of the same material incorporated by reference in the application as filed. Submitted with the Declaration are Exhibit A (a printed copy of the complete material incorporated by reference in the specification as filed), Exhibit B (a CD-ROM containing the complete material incorporated by reference in the specification as filed), and a notarized certification certifying that Exhibits A and B were downloaded from the website www.genome.we.mit.edu/MPR/CNS at 1:00 PM (EST) on Thursday, January 31, 2002. Thus, because the material added herein was incorporated by reference in the Specification as filed, no new matter has been added.

Amendments to the Claims

Applicants have amended Claims 1, 3, 4, 7, 12-14, 16-18, 24-26, and 31-32 and have cancelled Claims 2, 5, 6, 15, 30, 33 and 34 herein. The Claims have been amended to remove reference to non-elected subject matter and to recite the informative gene M64347; support for this amendment can be found, for example, in Tables 1 and 6 of the Substitute Specification as filed on June 7, 2002. No new matter has been added.

Objections to the Specification

The Examiner objects to the Specification because it contains embedded hyperlinks and/or other browser-executable code. Applicants have amended the Specification to remove active hyperlinks.

The Examiner also notes that the use of the trademark "GeneChip" should be capitalized throughout the specification. Applicants further note that the use of the trademark "GeneChip" is capitalized throughout the Specification, and is accompanied by suitable generic language. For example, on page 31, line 23, the term is followed by the generic "probe array". Elsewhere, the term "GENECHIP" is used to refer to proprietary software from Affymetrix that is used to analyze data obtained from such arrays.

In light of the above amendments and comments, reconsideration and withdrawal of the objection are respectfully requested.

Objections to the Claims

The Examiner objects to Claims 1-4, 7-9, 12-20 and 23-33, stating that (A) Claims 1-4, 7-9, 12-20 and 23-33 are drawn to non-elected genes; and (B) Claims 12 and 13 fail to further limit Claim 1; Claims 24 and 25 fail to further limit Claim 14; and Claims 28 and 29 fail to further limit Claim 26.

Applicants have amended the claims to reflect the elected subject matter. In response to the Examiner's assertion that Claims 12 and 13 fail to further limit Claim 1, Claims 24 and 25 fail to further limit Claim 14, and that Claims 28 and 29 fail to further limit Claim 26, Applicants respectfully disagree. Applicants have amended the claims to recite the elected gene (M64347_at); the election of this gene does not preclude the additional inclusion of other genes in the gene expression profile. Claims 12, 13, 24, 25, 28 and 29 merely further define these additional genes and clearly further limit the term "informative gene".

In view of the amendments made herein and the comments above, reconsideration and withdrawal of the objection to the Claims are respectfully requested.

Rejection of Claims 26-29 Under 35 U.S.C. §101

Claims 26-29 are rejected under 35 U.S.C. §101. Specifically, the Examiner asserts that Claim 26 relies on a hypothetical model of the relationship between the gene expression profile and class distinction that does not result in a tangible outcome, and as such, asserts that the invention is directed to non-statutory subject matter.

Applicants have amended Claim 26 to recite a tangible gene expression profile obtained from a sample. The claimed method therefore recites the comparison of a tangible sample to a model in order to make the class distinction. Therefore, the process does not consist solely of an abstract idea, and is in compliance with 35 U.S.C. §101. Applicants further note that Claims 27-29 depend from Claim 26, and are therefore also in compliance with 35 U.S.C. §101. Reconsideration and withdrawal of the rejection are respectfully requested.

Rejection of Claims 1-4, 7-9, 12-20 and 23-34 Under 35 U.S.C. §112, Second Paragraph

Claims 1-4, 7-9, 12-20 and 23-34 are rejected under 35 U.S.C. §112, second paragraph, for failing to point out and distinctly claim the subject matter that the Applicants regard as their invention.

Specifically, the Examiner asserts that Reference to "FGFR3 " is vague and indefinite because there can be more than one isoform of FGFR3. Further, the GenBank accession number M64347_at is variable because the sequence can be edited.

Applicants respectfully traverse this rejection. The test for definiteness is not, as the Examiner seems to suggest, a certain sense of immutability of the terms used, but rather, whether the claimed subject matter is described in such a way as to provide warning to one of skill in the relevant art of that which constitutes infringement. "The primary purpose of this requirement of definiteness of claim language is to ensure that the scope of the claims is clear so the public is informed of the boundaries of what constitutes infringement of the patent." (MPEP §2173)

Applicants assert that reference to the FGFR3 gene by its GenBank accession number is a sufficient description to allow one of skill in the art to precisely describe the FGFR3 gene in such a way as to render the claim definite. The National Center for Biotechnology Information describes the GenBank database as "An annotated collection of all publicly available nucleotide and amino acid sequences." (http://www.ncbi.nlm.nih.gov/About/tools/restable_nuc.html) This database is a resource recognized by one of skill in the art to be comprehensive and accurate. Referring to FGFR3 by its GenBank accession number is a common way of providing a link to the art-recognized sequence of the gene, and, as such, one of skill in the art would know with sufficient clarity how to use the sequence of the FGFR3 gene for the purposes of the claimed invention.

Additionally, Applicants point out that the FGFR3 gene itself is not claimed. The claims call for a determination of the expression from a particular gene, and this involves the measuring of gene expression products. Regardless of whether the sequence of M64347_at as provided by GenBank is edited or not, the gene expression product of the gene is clear to one of skill in the art. Possible sequence variations and the possible existence of FGFR3 isoforms in a genome do not render the gene expression profile indefinite; the measure of the gene expression product is a determinable and definite value. Expression levels are determinable irrespective of typographical

or other sequencing errors recorded in a publicly available databases. The gene expression profile of FGFR3 is a definite and determinable by the methods described in the Specification and known in the art.

The Examiner rejects the term "brain tumor type" in Claims 2 and 3, stating that it is unclear what this term refers to in Claim 1. Applicants have amended Claim 1 such that the ambiguity has been eliminated.

The Examiner rejects the term "medulloblastoma sub-type" in Claim 4 as lacking antecedent basis in Claim 3. Applicants have amended to 4, thereby obviating the rejection.

The Examiner rejects Claims 7 and 8 as not containing an active method step. Applicants point out that Claims 7 and 8 depend from Claim 1 and therefore contain the active method steps of Claim 1. Therefore, Claims 7 and 8 comply with 35 U.S.C. §112, second paragraph.

The Examiner rejects Claims 1, 14 and 31 for failing to show the relationship between steps b) and c). Applicants have amended Claims 1, 14 and 31, thereby obviating the rejection.

The Examiner rejects Claim 1, 32 and 33 as failing to correlate section c) with the preamble. Applicants point out that the gene expression profile of section c) is correlated with a particular phenotype described in the preamble. Therefore, section c) is related to the preamble in each of Claims 1 and 32. Claim 33 has been cancelled.

The Examiner rejects Claim 31 as not containing an active method step utilizing "drug candidates". Applicants have amended Claim 31, thereby obviating the rejection.

The Examiner rejects Claim 33 because "tumor class" lacks antecedent basis in the claim, and, further, that the outcome of the claim is inconsistent with the preamble. Applicants have cancelled the Claim, thereby obviating the rejection.

The Examiner rejects Claims 26 and 27, asserting that the metes and bounds cannot be determined without a recitation of the mathematical equation used for the determination of the weighted vote. Applicants have amended Claim 26. Applicants further refer the Examiner to the Specification, page 33, line 11 through page 34, line 6, where a particular weighted voting algorithm is described. Applicants further refer to the Specification as amended above for further details of algorithms used to identify informative genes and to correlate gene expression profiles with reference expression profiles. These sections clearly describe how a winning class is to be

determined and how gene expression values are used to determine votes that are later summed to determine the winning class.

Applicants point out that the claimed method of Claims 26 and 27 describes assigning a sample to a particular treatment outcome class (of which there can be more than one). Therefore, a_g is clearly described as the correlation between a gene's expression value and a particular member of the class. This value is a definite value assigning the relative importance of a gene for making a particular class distinction. One of skill in the art would be able to determine an empirical value for a_g that is definite. In order to determine b_g, one of skill in the art will be able to calculate b_g for a particular gene as defined in the Specification as, $b_g = (\mu_1(g) + \mu_2(g))/2$. Thus, b_g is determined by analyzing the expression of a gene in a first class and in a second class. The "first" and "second" class is determined by the skilled artisan according to the particular needs of the assays, as would be known to the skilled artisan. With respect to the term, "x_g", it is clearly recited to be the $\log_{10}$ gene expression value in the sample to be tested. It does not require a determination of "how a $\log_{10}$ gene expression value differs from the $\log_{10}$ gene expression level in the sample to be tested." (Page 6 of the Office Action). As amended, x_g can be determined using the gene expression products isolated in section a). It is the expression value of a gene in the sample. This is clearly recited in the Claim and in the Specification.

Applicants summarize by asserting that a weighted voting scheme is described in sufficient detail in the Specification to clearly indicate the metes and bounds of Claims 26 and 27. For the particular terms recited in Claim 27, is the correlation between gene expression values and class distinction; b_g is a term that is definite and relates to a gene's expression in each of two classes, as determined by the skilled practitioner wishing to make the distinction; and x_g is the expression value of the gene in the test sample. Furthermore, the Specification provides a method for determining a winning vote (positive or negative), and a summation of votes for more than one gene is also an unambiguous concept in light of a description of how the vote is to be determined. Thus, the metes and bounds of Claim 26, as amended, are clearly defined with respect to use of a weighted voting algorithm to determine a weighted vote. Such terms are both known in the art and described in the Specification.

In light of Applicants' amendments to the Claims and remarks, reconsideration and withdrawal of the rejections are respectfully requested.

Rejection of Claims 1-4, 7-9, 12-20, 23-29 and 34 Under 35 U.S.C. §112, First Paragraph

Claims 1-4, 7-9, 12-20, 23-29 and 34 are rejected under 35 U.S.C. §112, first paragraph, as containing subject matter that was not described in the Specification in such a way as to reasonably enable one skilled in the relevant art to make and/or use the claimed invention.

Applicants have amended the Claims to recite M64347_at.

Applicants note that the invention as claimed is directed to isolating a polynucleotide gene expression product from two or more genes, wherein one gene is M64347_at, and determining the gene expression profile. As described in the Specification, "gene expression products" are proteins, polypeptides, or nucleic acid molecules (*e.g.*, mRNA, tRNA, rRNA, or cRNA) that result from transcription or translation of genes (see, for example, page 9, lines 18-20). Applicants point out that it is the detection of gene expression products, not the gene itself, that leads to the creation of a gene expression profile.

The Examiner cites Thompson *et al.* and Abbass *et al.* as teaching various gene expression products, tissue-specific gene expression, and various isoforms of FGFR3. Applicants note that these references clearly demonstrate that one of skill in the art would know how to detect gene expression products of FGFR3, as, in fact, this is specifically taught by these references.

The Examiner asserts that Wren *et al.* teach that an allelic diversity exists for M64347_at. Applicants point out that M64347_at is but one gene out of dozens analyzed by Wren *et al.* in determining a frequency of repetitive elements in a genome. Disclosed are allelic variations in the 5' and 3' UTRs, as well as coding sequences. Wren *et al.* do not specifically disclose any allelic variation, *e.g.*, a polymorphism that affects the coding region of M64347_at, that would interfere with the detection of a gene expression product from M64347_at. Although repeats were found in several of the genes listed, there is no specific teaching of a polymorphism that would affect the detection of a gene expression product from M64347_at, and, therefore, there is no teaching demonstrating that one of skill in the art would need guidance beyond the disclosure of the Specification and that which was known in the art at the time of filing. Applicants note that the conclusions of Wren *et al.* are based on an aggregate of data obtained from several genes; no conclusions specific to M64347 are drawn, and no polymorphisms specific to M64347 are taught. However, even if such polymorphisms were taught, such a teaching would not affect the

ability of one of skill in the art to isolate a gene expression product of M64347 from a sample, as one of skill in the art would clearly be aware of the potential for allelic variation and employ detection methods that would be buffered from the effects of polymorphic variation (*e.g.*, by using probes that detect highly conserved mRNA sequences).

The Examiner asserts that there are no teachings in the Specification to correlate a value which is several standard deviations from the mean with a method of classifying a brain tumor or method of predicting the efficacy of a brain tumor. Applicants assert that such correlation methods, as described above, are known in the art and involve known and described statistical methods available at the time of filing. Applicants have amended the Specification to include such correlation methods. In the description og FIG.3, applicants state, "Figs. 3B and 3C are graphical and tabular representations of fifty genes most highly associated with favorable outcome (Fig. 3B) or with treatment failure (Fig. 3C) according to the signal-to-noise metric." A marker of treatment failure is certainly predictive of treatment outcome. Further, the inclusion of M64347 in a last of markers useful for determining risk of brain tumors is not necessarily incompatible with the use of the marker as a marker for treatment failure as well.

The Examiner asserts that the Specification does not teach the correlation of the expression profile of M64347 and rhabdoid tumor, primitive neuroectodermal tumor, pineoblastoma and glioblastoma. Applicants have cancelled Claims 2 and 15.

The Examiner further asserts that there is no guidance for a specific polynucleotide probe and hybridization conditions to be used in the determination of an expression profile. Applicants point out that the Specification discloses that "[t]he correlation between gene expression and class distinction can be determined using a variety of methods. Methods for defining classes and classifying samples are described, for example, in U.S. Patent Application Serial No. 09/544,627, filed April 6, 2000 by Golub *et al.*, the teachings of which are incorporated herein by reference in their entirety. The information provided by the present invention, alone or in conjunction with other test results, aids in sample classification." (page 13, 11-16)

In addition, Applicants disclose that "RNA obtained from patients was analyzed on Affymetrix (Santa Clara, CA) oligonucleotide arrays containing probes for 6817 genes as previously described (Tamayo, P. *et al.*, 1999. *Proc. Natl. Acad. Sci. USA.* 96:2907-2912)." (16, 8-12) And, further, "Since labeled targets hybridize, under appropriate stringency conditions

known to one of skill in the art, specifically to complementary oligonucleotides contained in the microarray, and since the sequence and position of each oligonucleotide in the array are known, the identity of the target nucleic acid applied to the probe is determined." (12, 21-25) Specific probe sequences and hybridization conditions had been previously disclosed and incorporated by reference. Therefore, Applicants have disclosed specific probes and hybridization conditions useful in practicing the methods of the claimed invention.

As discussed above, the specification describes parameters for determining a weighted vote and, as amended, additional details are incorporated into the specification to further clarify the state of the art at the time of filing.

In light of the remarks and amendments to the Specification and the Claims, reconsideration and withdrawal of the rejection are respectfully requested.

Rejection of Claim 30 Under 35 U.S.C. §102(b)

Claim 30 is rejected under 35 U.S.C. §102(b) as being anticipated by Levine *et al.* (WO 99/50456). Applicants have cancelled Claim 30, thereby obviating the rejection.

Rejection of Claims 32 and 33 Under 35 U.S.C. §102(e)

Claims 32 and 33 are rejected under 35 U.S.C. §102(e) as being anticipated by either of Au-Young *et al.* (U.S. Patent No.: 6,500,938) or Friend *et al.* (U.S. Patent No.: 6,218,122).

Applicants have cancelled Claim 33 and amended Claim 32 to recite M64347_at.

The Examiner states that Au-Young *et al.* do not teach the expression profile of M64347 or the FGFR3 encoded thereby. Applicants additionally point out that Friend *et al.* do not teach the use of M64347 or the FGFR3 encoded thereby.

Therefore, as neither Au-Young *et al.* nor Friend *et al.* teach every element of the claimed invention, as amended, reconsideration and withdrawal of the rejection are respectfully requested.

Rejection of Claim 31 Under §103(a)

Claim 31 is rejected under 35 U.S.C. §103(a) as being unpatentable over Au-Young *et al.* in view of Abbass *et al.* (1997, *J. Clin. Endocrinol. Metab.*, 82:1160-1166).

Applicants respectfully traverse this rejection. Applicants have amended Claim 31 to recite expression profiles derived from expression products of at least two informative genes, at least one of which is M64347_at. As Abbass *et al.* teaches only differential expression of FGF receptor, they do not teach every element of the claim as amended. Applicants further note that Abbass *et al.* do not teach a method for evaluating a drug candidate for its effectiveness in treating a brain tumor. Furthermore, Au-Young *et al.* do not provide informative genes useful in evaluating drug candidates effective in treating brain tumors.

As the teachings of Au-Young *et al.* in view of the teachings of Abbass *et al.* do not teach every element of Claim 31 as amended, they do not render Claim 31 obvious. Therefore, reconsideration and withdrawal of the rejection are respectfully requested.

CONCLUSION

In view of the above amendments and remarks, it is believed that all claims are in condition for allowance, and it is respectfully requested that the application be passed to issue. If the Examiner feels that a telephone conference would expedite prosecution of this case, the Examiner is invited to call the undersigned.

Respectfully submitted,

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